UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/557,262	04/24/00	ROSENBERG	R MIT-087

EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 11/08/01

021323
TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON MA 02110

HM12/1108

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

*U.S. GPO: 2000-473-000/44602

Office Action Summary	Application No. 09/557,262	Applicant(s) ROSENBERG ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *13-28 and 33-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-60 are pending in the instant application.

Election/Restrictions

1. Applicant's election with traverse of the invention of group I, set I (claims 1-12 and 29-32, pertaining to human and murine 3-OST-1 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that a search of any one of the claimed groups would necessarily include a search in the classes and subclasses relevant to each other claim groups. This is not found persuasive because, although, all the nucleic acids encoding animal proteins are grouped in one class/subclass, nucleic acids encoding distinct proteins with distinct amino acid sequences would have distinct nucleotide sequences and therefore, would require separate search in the sequence database. In the instant case, instant application is drawn to six patentably distinct nucleic acid molecules with distinct nucleotide sequence and each nucleic acid encodes a distinct protein (a human or murine 3-OST-1, human 3-OST2, human 3-OST3A, human OST-3B, human 3-OST4, and C.elegans ce-3-OST), with different sequence and domain structure, as noted in the office action of 7-6-01 (see page 2). Accordingly, the nucleic acid of each group would require separate search in the sequence database and such a search would not be coextensive with the search for the nucleic acids of other groups.

dac 11/5/01

The requirement is still deemed proper and is therefore made FINAL.

1. Claims 13-28 and 33-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

2. Claims 1-12 and 29-32 pertaining to human and murine 3-OST-1 are instantly under investigation.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The oath claims priority to the PCT/US98/ 22597 under 35 USC 119(a-d). Since the PCT is a US PCT, it should be listed for priority under 35 USC 120.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 29-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case the claimed invention encompasses any non-human transgenic animals (including rat, mice, hamster, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs, non-human primates, and invertebrates) that comprise an inserted nucleic acid encoding 3-OST-1 of any organism, allelic variants or transspecific allelic variants thereof, fragments of 3-

OST-1. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In this case, the specification provides prophetic examples and methodology to make transgenic animals (see pages 22-26). However, considering the fact that the claimed invention encompasses transgenic animals that comprise full length or various fragments of 3-OST-1 as well as knockout animals whose phenotypes and characteristics may not be known because the art of making transgenic animals or knockout animals is highly unpredictable.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of inactivating a gene or expressing a gene in an animal can not be predicted, particularly when a gene product may be interacting with the proteins of a family of proteins. For example, Korach et al (US Patent No. 5,650550) produced a knockout mouse lacking a functional estrogen receptor. One skilled in the art would not have predicted that such an animal would even be viable (see col 9, lines 22-39), much less have been able to predict the resulting phenotype. In the instant application, what would have been the result of expressing the recited nucleic acids or inactivation of a 3-OST-1 gene, in the transgenic animals encompassed by the invention is not known and the specification does not provide any description of the characteristics of the animal. With the limited information disclosed in the specification, an artisan would have not been able to predict whether all these animals would have had same or different phenotypes compared to the knockout mice or transgenic mice.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

6. Claims 1, 5, 6, and 8-12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

When the claims are analyzed in light of the specification, instant invention encompasses a nucleic acid that encodes a 3-OST-1 protein from any organism, allelic variants, transspecific variants, and sequences that have at least 60% sequence identity to SEQ ID NO 1 or SEQ ID NO 3, chimeras, etc. However, the specification discloses only SEQ ID NO 1 and 3 that encode the polypeptide disclosed in SEQ ID NO 2 and 4. The nucleic acid of SEQ ID NO 1 is a human sequence whereas the nucleic acid of SEQ ID NO 3 is a mouse sequence. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SEQ ID NO 1 and 3 are the only species whose complete structure is disclosed. The specification does not provide any disclosure as to what would have been the sequence of 3-OST-1 encoding nucleic acids from any other organisms or what would have been the structure of a representative species of the genus, for example, what would be the structure of a representative allelic variant or transspecific variant etc.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the identifying characteristics would be the sequence, presence of sulfotransferase specific motif and substrate specificity that distinguishes 3-OST-1 from other 3-OST proteins. However, the specification does not describe any characteristics that would specific to 3-OST-1 and that would be present in 3-OST-1 of other organisms or among allelic variants or transspecific allelic variants. In regard to

polynucleotides from species other than humans and mouse, it is noted that the specification does not provide any disclosure whether these sequences from other species would have had same characteristics would have had additional characteristics or properties.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of cDNAs besides SEQ ID NO 1 and 3 that encode the amino acid sequences disclosed in SEQ ID NO 2 and 4 respectively, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: (i) an isolated nucleic acid that encodes a human or mouse 3-OST-1 protein; (ii) an isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO 1 or SEQ ID NO 3; (iii) an isolated nucleic acid that encodes a mature murine or human 3-OST-1 protein; (iv) an isolated nucleic acid that encodes murine or human 3-OST-1 protein disclosed in SEQ ID NO 2 and SEQ ID NO 4 respectively; (v) an isolated nucleic acid that encodes a 3-O-sulfotransferase domain of the human or mouse 3-OST-1 protein wherein the domain consists of residue 53-311 of SEQ ID NO 2 or of residue 49-307 of SEQ ID NO 4; (vi) an isolated nucleic acid comprising at least 16 consecutive nucleotides of SEQ ID NO 1 or SEQ ID NO 3, and (vii) an isolated host cell selected from the group consisting of: bacterial cells, yeast cells, insect cells, and mammalian cells, wherein the mammalian cells are selected from the group consisting of: COS-7 cells, CHO, murine primary cardiac microvasculature endothelial cells, murine mast cell line C57.1, human primary endothelial cells or umbilical vein, F9 embryonal carcinoma cells, rat fat pad endothelial cells, and L cells, wherein the host cell comprises the nucleic acid, does not reasonably provide enablement for any and all 3-OST-1 encoding nucleic acids from any and all organisms, any and all fragments thereof, and any and all host cells and other recited embodiments encompassed by the claimed invention. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 29-32 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The invention as claimed encompasses nucleic acids that are 60% nucleotide sequence identity to SEQ ID NO 1 or SEQ ID NO 3 and encodes a functional fragment that has sequence specific binding to HIS or 3-O-sulfotransferase activity, any functional fragments of 3-OST-1 or, a nucleotide sequence that has synonymous substitutions in SEQ ID NO 1 or SEQ ID NO 3, any non-human transgenic animals (including rat, mice, hamster, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs, non-human primates and invertebrate animals) that comprise an inserted nucleic acid encoding 3-OST-1 of any organism, allelic variants or

transspecific allelic variants thereof, fragments of 3-OST-1, cells of the transgenic animals, embryonic stem cells, gametes, zygotes, and germ cell lines comprising the recited nucleic acids, however, the specification as filed does not provide sufficient guidance as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims. An artisan of skill would have required extensive experimentation to practice the claimed invention commensurate with the scope of the claims and such experimentations would have been considered because the art of making and using the claimed invention was unpredictable at the time of the invention and the experimentation required would not have been routine, as discussed below.

First, the specification is not enabling for the claimed nucleic acids that have at least 60% sequence identity with SEQ ID NO 1 or SEQ ID NO 3 or allelic variants or transspecific allelic variants of 3-OST-1 and host cells comprising said nucleic acids because the specification only teaches a nucleic acids that encode the polypeptides of SEQ ID NO 2 and 4. The issue is: how would an artisan of skill have made the all the nucleic acid molecules encompassed by the claimed invention, whether the proteins encoded by them would have had the biological activity of a 3-OST-1 protein as claimed and as to how an artisan of skill would have used these. For example, will any nucleic acid in which at least 40% of the nucleotide sequences disclosed in SEQ ID NO 1 and 3 have the biological activity and function of the wild type protein. These proteins would include mutants produced by deletion, substitution, and addition in the wild type polynucleotides such that up to 40% of nucleotides would be different from the sequence of SEQ ID NO 1 or 3. SEQ ID NO 1 contains 1685 nucleotides, which encodes for a protein of 311 amino acids whereas SEQ ID NO 3 contains 1305 nucleotides that encode a protein of 307 amino acids. A change in 40% of SEQ ID NO 1 would be 672 nucleotides that would encode 225 amino acids which indicates every other amino acid or more than two third amino acid residues could be changed. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see

second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). The specification does not teach which changes in the nucleotide sequence of SEQ ID NO 1 or 3 would encode a amino acid sequences (due to allelic variations or changes or mutation) that would retain the function of the human or murine 3-OST-1. The specification does not teach how to use a nucleic acid that would have encoded a protein, which was derived from the protein of SEQ ID NO 2 or of SEQ ID NO 4 but did not have the function of the starting protein. Alternatively, the specification does not teach how would an artisan have made a polynucleotide that would have encoded a protein in which every other amino acids would have been changed but the protein would have retained the function of the starting protein. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Even if these polynucleotides were to be used as a probe, they will not be able to specifically recognize a related polynucleotide or the polynucleotide of SEQ ID NO 1 or SEQ ID NO 3. Alternatively, the protein encoded by such polynucleotides would not recognize the protein of SEQ ID NO 2. Similar arguments will also be applicable to any fragments of the nucleotides that encode fragments of SEQ ID NO 2 or SEQ ID NO 4 or any fragments of any and all 3-OST-1. If one used degenerate nucleotides for every amino acid in the protein, resultant polynucleotide would not hybridize to a sequence of SEQ ID NO 1 or 3. Alternatively, if it is not

known whether the protein encoded by these polynucleotides did not have the biological activity, how can they be used and for what?

As discussed above, the human and murine 3-OST-1 proteins consists of 311 and 3-7 amino acids respectively, and it is not clear as to which of these amino acids could be substituted for a biologically similar amino acid and it is not clear where modifications (in allelic variants or in mutants) may be tolerated while predictably retaining the activity of the protein. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity of the protein of interest. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol. 247, pp. 1306-1310, especially p. 1306, column 2, paragraph 2; and see Ngo et al, The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz er (ed.), pages 433&492-495; and Frommel et al/1985). Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant amino acid substitutions and the nature and extent of changes that can be made in these positions in order to obtain protein that retain function. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention.

Next the question is: is the claimed invention enabled for any fragment of 3-OST-1? It is noted that the claims recite a nucleic acid sequence comprising a nucleotide sequences amino acid residues 21-52, 260-269, 250-276, 53-311 or 21-

307 of SEQ ID NO 2 or 21-48, 256-265, 246-272, 49-307 or 21-303 of SEQ ID NO 4. The specification indicates that 21-52 in SEQ ID NO 2 and 21-48 in SEQ ID NO 4 correspond to SPLAG domain, however, the specification does not teach as to what is the function of the fragment or a sequence that encodes an amino acid that has 60% sequence similarity with these peptides or what is the use of these fragments. The specification discloses that aa 53-311 of SEQ ID NO 2 and 49-307 are the minimal fragments that are necessary for sulfation activity (see lines 20-26 on page 13). However, the specification does not teach as to what is the function of other recited fragments and as to what would be the use of these fragments. In other words, the specification does not provide any guidance as to how to use the recited fragments except for the 53-311 of SEQ ID NO 2 or 49-307 of SEQ ID NO 4 and therefore, an artisan of skill would have required extensive experimentation to determine the function of the fragments and devise an assay to determine the function because the specification discloses that the only fragment that works with the assay system disclosed in the specification is 53-311 of SEQ ID NO 2 and 49-307 of SEQ ID NO 4. Regarding the sequence recited in claim 6 (i) it is noted that it is unclear as to what would be the function of a chimera of nucleic acid of a with that of h or b with h because the sequence of a is a peptide whereas that of h is a sequence that has 60% sequence similarity with the sequence of a. The specification does not teach how to use such a sequence.

Additionally, if the specification is not enabling for the claimed nucleic acids, it would not be enabling for the claimed host cells because if an artisan did not know what was the function of the protein encoded by the claimed polynucleotide, how would an artisan know, how to use such host vectors comprising the nucleic acids. Furthermore regarding claims 8-12, it is noted that the specification is not enabling for embryonic stem cells, zygotes, gametes, germ cell lines and transgenic animal cells because the art of making these cells was unpredictable at the time of the invention and the specification as filed did not provide sufficient guidance as to how to make these cells and use them. For example, the art of culturing and maintaining ES cells in culture is unpredictable. Gardner and Brook (Gardner RL and Brook FA. International J. of Dev. Biol. 41:235-243, 1997) summarized the

progress in the field of ES cell biology, "Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most stains have so far proved refractory to the derivation of cell lines....." Additionally, gene targeting and selection of the ES cells that harbor the integration of a desired construct also has been shown to be unpredictable in animals other than mice. To prevent their differentiation, ES cells are maintained in culture in the presence of mouse derived factors that inhibit differentiation either by coculturing the cells in the presence of feeder cell lines or by adding agents to the culture as a media supplement. However, it has been suggested that the such differentiation-inhibitory derived from mouse do not adequately prevent differentiation of stem cells in species other than the mouse. Additionally, the art of transgenesis based on ES cells is unpredictable. Seamark (Seamark, Reprod. Fertil. Dev. 6: 653-657, 1994) states that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract on page 653). He further adds that although various studies have provided insight into what this new technology could offer to the livestock breeder, scientific and technical challenge still confront the molecular and reproductive biologist attempting to make the technology available to serve this purpose (page 653, 3rd paragraph). Likewise, the art of making gametes comprising nucleic acids was also not predictable at the time of the invention. For example, making transgenic animals using sperms as the carrier of a transgene was unpredictable at the time of the invention. Gandolfi (Transgenic Research 7:147-155, 1998), while reviewing the art of transgenesis, stated, "The stable integration of exogenous genes into the genome of adult animals mediated by sperm cells is a very rare event, although several reports describe forms of partial success. Available evidence suggests that changes to the DNA molecules, occurring mostly within the oocyte, using spermatozoa as vectors of exogenous genes." The specification does not provide any guidance as to how an artisan of skill would have produced a transgenic animal using gametes or sperms that comprised the recited nucleic

acids. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. Investigators observed 5-70 fold lower yields of a recombinant protein in transgenic mice when they used a construct designed for expression in sheep (see lines 1-12 in 4th para of col 1 on page 632 in Mullins et al. (Mullins JJ et al. Hypertension 22:630-633,1993)). The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors. In a more recent assessment of the transgenic technology, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in non-targeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression). Introduction of foreign DNA into fertilized oocyte, for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable.

The specification on page 22-26 discloses general information regarding producing transgenic animals, however, the specification does not provide any specific guidance, as how to produce a transgenic animal, as to what vector would be used, etc. and as discussed above there are several limitations in making of transgenic animals and the specification does not teach as to how an artisan of skill would have resolved these limitations. While the making of a transgenic mouse has become more routine, one can not predict the phenotype of a transgenic mouse comprising a nucleic acid because of the limitations discussed above and in the absence of a phenotype, an artisan would not know how to use the transgenic animals, even a transgenic mouse. The specification does not provide as to what would have been the phenotype or characteristics of a transgenic animal or a transgenic mouse or a transgenic invertebrate which comprises the 3-OST-1 of SEQ ID NO 1 or 3 and in the absence of a phenotype, how would an artisan use the transgenic animals, including the transgenic mouse or the cells of such transgenic animal. It is noted that claims 29 and 30 recite animal models wherein not only 3-OST sequence is inserted in the genome of the animal, but these claims recite fragments of 3-OST, allelic variants, knockout animals, as well as those which have different domains of 3-OST. Again, there is not guidance or disclosure in the specification as to what would have been the phenotype of all these animals encompassed by the claimed invention and whether any of these animals would have even survived.

Regarding the knockout transgenic animals, it is noted that one may not even predict whether a transgenic mammal in which endogenous 3-OST-1 gene was inactivated would have been viable due to the unpredictability of the effect of blocking the function of a gene that may interact with other genes. Furthermore, with regard to the transgenic animals in which a DNA construct comprising 3-OST-1 regulatory sequences directing the expression of a reporter gene was integrated in the genome, the specification does not teach any guidance s to what sequences would be used in the 3-OST-1 regulatory sequences, what is the structure of the 3-OST-1 promoter, and what would be the effect of integrating such a construct in the

genome of a transgenic animal, what would be the phenotype of the animals and in the absence of a phenotype, how would an artisan know how to use such animals.

Therefore, the specification fails to provide any guidance as to how an artisan would have dealt with the art recognized limitations of the method for making any and all transgenic animals and therefore, the creation of any and all non-mouse animals would have necessitated undue experimentation on the part of an artisan because the art of making transgenic animals at the time of the invention was unpredictable and the experimentation required was not routine.

Furthermore, the specification fails to provide sufficient guidance as to how an artisan of skill would have made and used the claimed nucleic acids and host cells comprising the recited nucleic acids commensurate with the scope of the claims as discussed above and therefore, limitation of the scope of the claimed invention as discussed above is proper.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-12 and 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12 and 29-32 are indefinite because they recite invention not elected for prosecution. It is noted that the invention elected for prosecution is 3-OST-1 from human and mouse and the nucleic acids SEQ ID NO 1 and SEQ ID NO 3. Applicants are advised to amend the claims to reflect the elected subject matter. Furthermore, claim 3 recites an improper markush group because it is missing "and" between the last recited species.

Claims 2-12 and 30-32 are vague and indefinite because these claims are dependent claims (dependent on claims 1, 8 and 29), but recite "a nucleic acid", "a host cell" or "a non-human animal model". Using the article "a" indicates an item out of a group of items, however the independent claims on which these claims are

dependent also recite terms "a nucleic acid", "a host cell" or "a non-human animal model", therefore, it is unclear whether the dependent claims recite the same invention as those of the independent invention or a different invention.

Claims 2-6 are indefinite because they recite the term "said nucleic acids", however, it is unclear as to which nucleic acids the term refers to since the term "a nucleic acid" has been recited both in the independent claim (claim 1) and dependent claims (2-6).

Claims 9-12 are indefinite because they recite the term "said cell" or "said host cell", however, it is unclear as to which cell the term refers to since the term "a host cell" has been recited both in claim 8 (where the term a host cell is used for the first time) and in claims (9-12).

Claim 5 is vague and indefinite because it uses the phrase "...comprises a nucleotide selected from nucleotide sequences within:" and it is unclear as to what is meant by this phrase, does it mean a nucleotide sequence within SEQ ID NO 1 or SEQ ID NO 3 or other recited sequences or what is encompassed by the claim and therefore, the metes and bounds of the claimed invention is not clear.

Claim 29 recites the limitation "said recombinant construct" in line 2. There is insufficient antecedent basis for this limitation in the claim because " a recombinant construct" has not been recited before. It is noted that the first two lines of the claim do not represent a complete thought.

Claims 31 and 32 are vague and indefinite because it is unclear as to which animal in the claim is being referred to by the term "said animal" since both the independent (claim 29) as well as the dependent claims (claims 31-32) recite the term "an animal".

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Marra et al (EST database accession no. WW62484, 6-7-96).

Marra et al teach a nucleic acid that has 100% sequence similarity over a region of 490 nucleotides (see the sequence comparison results) of SEQ ID NO 1. The sequence of Marra et al would also encode the polypeptide 260-269 of SEQ ID NO 2 (see the sequence comparison results).

Accordingly, the nucleic acid of Marra et al anticipates the nucleic acid of claim 7.

12. Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Philippsen et al (US 6239264, effective filing date 12-31-96).

The SEQ ID NO 906 in the cited US patent has a 100% sequence similarity with a region of 18 nucleotides of SEQ ID NO 3 (see the sequence comparison results). Accordingly, the invention of claim 7 anticipated by US 6239264.

13. Claim 7 is rejected under 35 U.S.C. 102(a) as being anticipated by Hillier et al (EST database accession no. AA460705, 6-9-97).

Hillier et al teach a 381 nucleotide long nucleic acid that has 100% sequence similarity with a region of 381 nucleotides of SEQ ID NO 3. Therefore, the nucleic acid of Hillier et al anticipates the nucleic acid of claim 7.

14. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Marra et al (EST database accession no. AA041885, 9-3-96).

Marra et al teach a nucleic acid that has 100% sequence similarity over a region of 508 nucleotides (see the sequence comparison results) of SEQ ID NO 1.

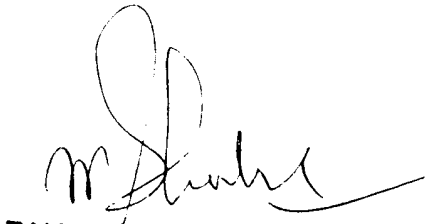
Accordingly, the nucleic acid of Marra et al anticipates the nucleic acid of claim 7.

15. The article by Liu et al (The Journal of Biological Chemistry 271:27072-27082, 1996) is noted. This article teaches purification of 3-O-sulfotransferase enzyme from LTA cells. The article by Shworak et al (The Journal of Biological Chemistry 272:28008-28019, 1999) is also noted. This article teaches the molecular cloning and expression of murine and human cDNAs encoding 3-OST-1. Both the articles are listed in the IDS.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.



RAM R. SHUKLA, PH.D
PATENT EXAMINER